ONCOIMMUNOLOGY
2021, VOL. 10, NO. 1, e1865653 (10 pages)
https://doi.org/10.1080/2162402X.2020.1865653

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ORIGINAL RESEARCH

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Pembrolizumab as a monotherapy or in combination with platinum-based chemotherapy in advanced non-small cell lung cancer with PD-L1 tumor proportion score (TPS) ≥50%: real-world data

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ABSTRACT

Both pembrolizumab (P) and combination of pembrolizumab with platinum-based chemotherapy (PCT) represent standard 1st-line options for advanced non-small cell lung cancer (aNSCLC) with PD-L1 tumor proportion score (TPS) ≥50%. The two strategies have never been compared in a randomized trial. 256 consecutive patients with *EGFR/ALK/ROS1*-wild-type PD-L1 TPS ≥50% aNSCLC receiving P (group P, n = 203) or PCT (group PCT, n = 53) as a 1st-line treatment were identified in the electronic databases of 4 Israeli cancer centers. Time-to-treatment discontinuation (TTD) and overall survival (OS) were assessed. Baseline characteristics were well balanced, except for age and ECOG PS differences in favor of group PCT. Median (m)TTD was 4.9 months (mo) (95% CI, 3.1–7.6) *vs* 8.0mo (95% CI, 4.7–15.6) (*p*-0.09), mOS was 12.5mo (95% CI, 9.8–16.4) *vs* 20.4mo (95% CI, 10.8-NR) (*p*-0.08), with P and PCT, respectively. In the propensity score matching analysis (n = 106; 53 patients in each group matched for age, sex and ECOG PS), mTTD was 7.9mo (95% CI, 2.8–12.7) *vs* 8.0mo (95% CI, 4.7–15.6) (*p*-0.41), and mOS was 13.3mo (95% CI, 6.8–20.3) *vs* 20.4mo (95% CI, 10.8-NR) (*p*-0.18), with P and PCT, respectively. Among various subgroups of patients examined, only in females (n = 86) mOS differed significantly between treatments (10.2mo (95% CI, 6.8–17.2) with P *vs* NR (95% CI, 11.4-NR) with PCT; *p*-0.02). In the real-world setting, no statistically significant differences in long-term outcomes with P *vs* PCT were observed; a prospective randomized trial addressing the comparative efficacy of P and PCT in different patient subgroups is highly anticipated.

List of abbreviations: *AE - adverse events; ALK - anaplastic lymphoma kinase gene; ALT - alanine aminotransferase; (a)NSCLC - (advanced) non-small cell lung cancer; AST - aspartate aminotransferase; BRAF - v-Raf murine sarcoma viral oncogene homolog B; BRCA2 - BReast CAncer gene 2; c-Met - tyrosine-protein kinase Met; CTCAE, v. 4.03 - Common Terminology Criteria for Adverse Events, version 4.03; CTLA-4 - cytotoxic T-lymphocyte-associated protein 4; ECOG PS - Eastern Cooperative Oncology Group performance status; EGFR - epidermal growth factor receptor gene; FISH - fluorescent in situ hybridization; HER2 - human epidermal growth factor receptor 2; IC - tumor-infiltrating immune cells; ICI - immune check-point inhibitors; IHC - immunohistochemistry; IQR - interquartile range; irAE - immune related adverse events; ISCORT - Israeli Society for Clinical Oncology and Radiotherapy; KRAS - Kirsten rat sarcoma viral oncogene homolog; (m)TTD -(median) time-to-treatment discontinuation; mo - months; (m)OS - (median) overall survival; (m)PFS - (median) progression-free survival; muts/Mb - mutations per megabase; NA - not specified/not available; NOS - not otherwise specified; NR - not reported/not reached; ORR - objective response rate; P - pembrolizumab; PCR - polymerase chain reaction; PCT - combination of pembrolizumab with platinum-based chemotherapy; PD – progression of disease; PD-1 - programmed cell death-1; PD-L1 - programmed cell death ligand-1; pts - patients; RET - proto-oncogene RET; ROS1 - proto-oncogene tyrosine-protein kinase ROS1; SD - standard deviation; STK11 - serine/threonine kinase 11; TC - tumor cells; TMB - Tumor mutation burden; TPS - tumor proportion score.*

ARTICLE HISTORY
Received 24 October 2020
Revised 8 December 2020
Accepted 10 December 2020

KEYWORDS
Pembrolizumab; pembrolizumab chemotherapy; PD-L1; real world; lung cancer

Introduction

Efficacy of anti-PD-1 (programmed cell death-1)/anti-PD-L1 (programmed cell death ligand-1) immune check-point inhibitors (ICI) in treatment-naive advanced non-small cell lung cancer (aNSCLC) – both as a single-modality approach and as a combination with platinum-based chemotherapy – has been proven in several large randomized controlled trials.[1–11] A positive correlation between the level of PD-L1 expression in the tumor cells and ICI efficacy has been observed. Tumors

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supplemental data for this article can be accessed here.

with high PD-L1 expression (e.g., tumor proportion score (TPS) ≥50% as assessed using 22C3 PharmDx assay,[12] and PD-L1 expression of either ≥ 50% on tumor cells (TC), or ≥ 10% on tumor-infiltrating immune cells (IC) using Ventana SP142 assay[6]) derive the largest benefit from anti-PD-1/anti-PD-L1 ICI.[3–5,7,8,10–13] Moreover, this is the only category of tumors in which the superiority of anti-PD-1/PD-L1 ICI over platinum-based chemotherapy has been demonstrated, allowing their use as a single-modality treatment, and not necessarily in combination with platinum-based chemotherapy.[1–3,6,10] Currently, the treatment approach in this patient subset is based on clinical discretion, and both ICIs as a single-modality and their combinations with platinum-based chemotherapy are considered standard of care.

The comparative efficacy of anti-PD-1/PD-L1 ICI administered alone or in combination with platinum-based chemotherapy in aNSCLC with PD-L1 TPS ≥50% has never been tested in a randomized controlled trial. According to the cross-trial comparison in this patient subset, the two treatment modalities are associated with similar long-term outcomes, and specifically, 1-year survival rates of 63–73%, 2-year survival rates of 45–52%, and median overall survival (mOS) of 20–30 months.[2–5,10,14–16] The main advantage of the combined modality here appears to be the superior objective response rate (ORR) of 61–64%, as opposed to 39–45% observed with ICI alone.[1,3,10,11,14,15] Superior ORR rates (RR, 95% CI – 1.62, 1.18–2.23, *p*-0.003) along with the superior progression-free survival (PFS) (HR, 95% CI – 0.55, 0.32–0.97, *p*-0.037) with the combined modality approach, as compared to pembrolizumab, have also been demonstrated in the meta-analysis using indirect comparison of the data retrieved from the randomized controlled trials.[17] The same meta-analysis confirmed the lack of OS advantage with the combined modality approach over pembrolizumab alone (HR, 95% CI – 0.76, 0.51–1.14, *p*-0.184). Another meta-analysis addressing several aspects of ICI application in aNSCLC, indicated similar long-term efficacy of ICI and the combination in the subset of tumors with PD-L1 TPS ≥50% (similar median OS, OS at 6 months, OS at 12 months and PFS at 12-months with p-0.184, 0.117, 0.351, and 0.498 for the interaction, respectively).[17] In the latter meta-analysis, the two strategies only differed in terms of short-term efficacy (median PFS, PFS at 6 months and ORR, with p-0.038, 0.002, and 0.009 for the interaction, respectively).[18] Importantly, because of the methodological issues associated with the indirect comparison and the analysis of published results and not of individual patients' data, conclusions of these meta-analyses are only hypothesis-generating. Additional network meta-analysis of twelve randomized clinical trials also demonstrated similar OS benefit (HR for the indirect comparison, 95% CI – 0.73, 0.50–1.05, *p*-0.087) and larger PFS benefit (HR for the indirect comparison, 95% CI – 0.52, 0.38–0.70, $p < .001$) in favor of the combination of pembrolizumab and platinum-based chemotherapy as compared to pembrolizumab alone in the subgroup of aNSCLC with PD-L1 TPS ≥50%.[19]

The main downside of incorporating platinum-based chemotherapy in the combined treatment is the chemotherapy-associated toxicity profile which typically includes myelosuppression, anemia, nausea and mucositis.[2,3,6] This argument further supports the preferential use of the ICI alone for the majority of aNSCLC with PD-L1 TPS ≥50%, while reserving the combinations of ICI with platinum-based chemotherapy for the symptomatic patients with large tumor burden and rapidly progressing tumors.

Facing the lack of the comparative data from the randomized clinical trials, we conducted a retrospective analysis of consecutive patients with epidermal growth factor receptor gene (*EGFR*)/anaplastic lymphoma kinase gene (*ALK*)/proto-oncogene tyrosine-protein kinase *ROS1* (*ROS1*)-wild-type PD-L1 TPS ≥50% aNSCLC treated with 1st-line pembrolizumab or the combination of pembrolizumab and platinum-based chemotherapy at four tertiary Israeli cancer centers. This analysis represents the real-world comparative evidence for the application of 1st-line pembrolizumab versus the combination of pembrolizumab and platinum-based chemotherapy as a 1st-line treatment. Our analysis included both efficacy and toxicity comparison of the two treatment approaches; an attempt to analyze the efficacy in several clinically important subgroups has been made.

Materials and methods

Patient selection

Consecutive patients with histologically confirmed advanced-stage (stage IV or stage III disease not amenable for definitive treatment) NSCLC with *EGFR/ALK/ROS1*-wild-type tumors and PD-L1 TPS ≥50% who have been treated with 1st-line pembrolizumab (P) or 1st-line combination of pembrolizumab with platinum-based chemotherapy (PCT) were identified through electronic databases of four Israeli cancer centers. Patients that initiated therapy between June 2016 and January 2020 were included; the cutoff data for data collection was January 28, 2020.

Study design and assessments

The patients were categorized to two groups according to the type of 1st-line treatment: group *P* – patients treated with 1st-line pembrolizumab (P); group PCT – patients treated with 1st-line combination of pembrolizumab with platinum-based chemotherapy (PCT).

Patients' charts and hospital electronic medical records were retrospectively reviewed, and baseline demographic, clinical, pathologic and treatment characteristics were retrieved. OS, time-to-treatment discontinuation (TTD) with P and PCT, and adverse events reported as related to treatment were assessed and compared between the groups P and PCT. A propensity score matching analysis was performed, and the patients in the two groups were matched for age, sex, and Eastern Cooperative Oncology Group performance status (ECOG PS); OS and TTD were compared between the matched groups as well. Additionally, OS and TTD were assessed in several selected subgroups according to age, sex, smoking status, ECOG PS, PD-

L1 TPS (90%>TPS≥50% and PD-L1 TPS ≥90%), and presence or absence of liver and brain metastases. Univariate analysis of impact of patient baseline characteristics, tumor and treatment characteristics on OS and TTD was performed.

TTD was calculated from 1st-line treatment initiation until 1st-line treatment discontinuation for any reason, including disease progression (PD), treatment toxicity, or death; the outcome was censored if a patient was alive and continuing the 1st-line treatment at the time of last follow-up. OS was calculated from 1st-line treatment initiation until death; the outcome was censored if a patient was alive at the time of last follow-up. The safety profiles of P and PCT were graded using Common Terminology Criteria for Adverse Events, version 4.03 (CTCAE, v. 4.03).[20]

Statistical analysis

The sample size was determined by the available patients meeting the inclusion criteria. The statistical analysis was generated using SAS Software, version 9.4.[21] Categorical variables were presented by numbers and percentiles; for continuous variables – medians and ranges or means and standard deviations (SD) were reported. A propensity score matching analysis was performed, and the patients in the two compared groups were matched for age, sex, and ECOG PS. OS and TTD were assessed by the Kaplan-Meier method, with the log-rank test for the comparison. Duration of follow-up was calculated by the reverse Kaplan-Meier method, with the log-rank test for the comparison. The Cox proportional-hazards regression model was used for univariate analyses of OS and TTD. Two-sided p values less than 0.05 were considered statistically significant.

Results

Patient and tumor characteristics

Two hundred fifty-six patients with *EGFR/ALK/ROS1*-wild-type aNSCLC and PD-L1 TPS ≥50% treated with 1st-line pembrolizumab with or without platinum-based chemotherapy in 2016–2020 were identified through electronic databases of four Israeli cancer centers (Thoracic Cancer Service, Davidoff Cancer Center, Rabin Medical Center, Beilinson Campus, n = 108; Thoracic Oncology Service, Institute of Oncology, Sheba Medical Center, Tel HaShomer, n = 77; Thoracic Cancer Service, Rambam Health Care Campus, n = 63; Oncology Department, Hadassah Medical Center, n = 8). Of 256 patients, 203 patients were treated with 1st-line pembrolizumab (group P), and 53 patients were treated with 1st-line combination of pembrolizumab with platinum-based chemotherapy (group PCT).

Baseline demographic, clinical and pathologic characteristics for the 256 included patients are displayed in Table 1. The selected cohort was mainly comprised of smokers; adenocarcinoma histology predominated; females comprised 32% and 42% of patients, in groups P and PCT, respectively (p-0.19). Patients in group PCT tend to be younger (mean age (SD) – 64.3 (9.8)), as compared to group P (mean age (SD) – 68.4 (10.6)) (p-0.02). Group PCT included more patients with ECOG PS 0/1 (85%) as compared to group P (68%) (p-0.02). No other significant differences in baseline patient and tumor characteristics between the groups were observed.

Molecular tumor testing was limited; the routine assessment (in accordance with pembrolizumab labeling) only included testing for common mutations in the *EGFR* gene (by either real-time polymerase chain reaction (PCR) using Cobas® *EGFR* test, or next-generation sequencing), *ALK* rearrangements (by either IHC using D5F3 CDx Assay, or Fluorescent *in situ* hybridization (FISH), or next-generation sequencing), and *ROS1* rearrangements (by either FISH, or next-generation sequencing). None of the included patients were diagnosed with an *EGFR* sensitizing mutation, *ALK* or *ROS1* rearrangement. Other molecular aberrations which were diagnosed are reported in the Supplementary Table S1.

Tumor mutation burden (TMB) testing using FoundationOne™ algorithm[22] was performed in four patients in group P, and TMB comprised 10 mutations per megabase (muts/Mb) in two patients, 38 muts/Mb and 8 muts/Mb – in one patient each. None of the tumors were tested for microsatellite instability/mismatch repair deficiency.

Considering the imbalances in terms of age and ECOG PS between the groups in the initial cohort (Table 1), a propensity score matching analysis was performed, and the patients in the two groups were matched for age, sex, and ECOG PS. The matched cohort (n = 106) included 53 patients in each group (Table 1). No significant differences in baseline patient and tumor characteristics between the matched groups were observed.

Treatment characteristics

The majority of patients in group PCT received pembrolizumab in combination with carboplatin/pemetrexed (n = 27); the second most commonly used chemotherapy backbone regimen was carboplatin/paclitaxel (n = 20); one patient received pembrolizumab in combination with cisplatin/pemetrexed; five additional patients received other chemotherapy regimens. For the pemetrexed – and paclitaxel-based combinations, standard protocols were used;[4,5] carboplatin or cisplatin treatment was delivered with a median dose reduction of 15% (range, 0%-80%), and the second compound in the chemotherapy regimen was delivered with a median dose reduction of 0% (range, 0%-80%). Pembrolizumab was delivered at a standard dose of 200 mg every 3 weeks;[3,12] no modifications to pembrolizumab dose have been reported.

With median follow-up of 22.3 months [Interquartile range (IQR), 14.5–28.9] for group P and 9.1 months [IQR, 5.6–15.8] for group PCT, (p < .0001 for the comparison), 78% (158/203) of group P and 53% (28/53) of group PCT discontinued the 1st-line treatment. The treatment was stopped for PD or death in 123 patients in group P and 19 patients in group PCT; other reasons for stopping the treatment were: planned treatment discontinuation after two years and intolerable toxicity. No significant differences were seen between the groups regarding

Table 1. Baseline and treatment characteristics of patients with advanced non-small cell lung cancer and PD-L1 tumor proportion score ≥50% treated with 1st-line pembrolizumab (P) or combination of pembrolizumab with platinum-based chemotherapy (PCT).

	All pts in the cohort (n = 256)			Pts matched for age, sex, ECOG PS (n = 106)		
	Pts treated with P (n = 203)	Pts treated with PCT (n = 53)	p value	Pts treated with P (n = 53)	Pts treated with PCT (n = 53)	p value
Age, years – mean (SD)	68.4 (10.6)	64.3 (9.8)	0.02	65.6 (8.6)	64.3 (9.8)	0.46
Sex, n (%)			0.19			1.00
Female	64 (32)	22 (42)		22 (42)	22 (42)	
Male	139 (68)	31 (58)		31 (58)	31 (58)	
Smoking history, n (%)			0.78			0.27
Current/past smoker	185 (91)	47 (89)		51 (96)	47 (89)	
Never smoker	16 (8)	5 (9)		2 (4)	5 (9)	
NA	2 (1)	1 (2)		0 (0)	1 (2)	
Histological subtype, n (%)			0.47			0.94
Adenocarcinoma	159 (78)	38 (72)		39 (74)	38 (72)	
Squamous-cell	33 (16)	10 (19)		10 (19)	10 (19)	
NSCLC NOS/other	11 (6)	5 (9)		4 (7)	5 (9)	
Stage, n (%)			0.72			0.24
IV	194 (96)	50 (94)		53 (100)	50 (94)	
III (not amenable for definitive treatment)	9 (4)	3 (6)		0 (0)	3 (6)	
ECOG PS at diagnosis, n (%)			0.02			1.00
0/1	137 (68)	45 (85)		46 (87)	45 (85)	
2/3/4	63 (31)	8 (15)		7 (13)	8 (15)	
NA	3 (1)	0 (0)		0 (0)	0 (0)	
Weight loss of more than 5%, n (%)			0.71			0.15
Yes	53 (26)	17 (32)		9 (17)	17 (32)	
No	85 (42)	23 (43)		28 (53)	23 (43)	
NA	65 (32)	13 (25)		16 (30)	13 (25)	
Brain metastases, n (%)			1.00			0.30
Yes	54 (26)	14 (26)		20 (38)	14 (26)	
No	148 (73)	39 (74)		33 (62)	39 (74)	
NA	1 (1)	0 (0)		0 (0)	0 (0)	
Liver metastases, n (%)			1.00			0.77
Yes	26 (13)	6 (11)		8 (15)	6 (11)	
No	177 (87)	47 (89)		45 (85)	47 (89)	
PD-L1 TPS*, n (%)			1.00			1.00
≥90%	32 (16)	11 (21)		9 (17)	11 (21)	
<90%	68 (33)	24 (45)		21 (40)	24 (45)	
NA**	103 (51)	18 (34)		23 (43)	18 (34)	
Received subsequent systemic treatment, n (%)	26 (13)	6 (11)	0.50	6 (11)	6 (11)	1.00
Subsequent chemotherapy, n (%)	22 (11)	5 (9)	0.62	6 (11)	5 (9)	0.75
Subsequent ICI, n (%)	6 (3)	2 (4)	1.00	0 (0)	2 (4)	0.49
Subsequent targeted therapy, n (%)	1 (0.5)	1 (2)	0.43	0 (0)	1 (2)	1.00

* *PD-L1 TPS was assessed by IHC using 22C3 PharmDx antibody) (10)*

** *PD-L1 TPS ≥50%, exact number not specified*

Abbreviations: ECOG PS – Eastern Cooperative Oncology Group performance status score; ICI – immune check-point inhibitors; IHC – immunohistochemistry; NA – not specified/not available; NOS – not otherwise specified; NSCLC – non-small cell lung cancer; P – pembrolizumab; PCT – combination of pembrolizumab with platinum-based chemotherapy; PD-L1 – programmed-death ligand 1; pts – patients; SD – standard deviation; TPS – tumor proportion score.

next-line treatments. Only 26 patients in group P (13% of the 203 patients in this group, and 21% of the 123 patients who progressed or died while on P) and 6 patients in group PCT (11% of the 53 patients in this group, and 32% of 19 patients who progressed or died while on PCT) received any subsequent systemic treatment (Table 1).

OS and TTD

During the study period 57% of group P and 30% of group PCT have died. Median OS was 12.5 months (95% CI, 9.8–16.4) in group P and 20.4 months (95% CI, 10.8-NR) in group PCT (p-0.08 for the comparison). Median TTD was 4.9 months (95% CI, 3.1–7.6) in group P and 8.0 months (95% CI, 4.7–-15.6) in group PCT (p-0.09 for the comparison) (Figures 1A, 1B).

In the matched cohort, median OS was 13.3 months (95% CI, 6.8–20.3) in group P and 20.4 months (95% CI, 10.8-NR) in group PCT (p-0.18 for the comparison), reflecting a non-significant trend for better OS in group PCT as compared to group P. Median TTD was 7.9 months (95% CI, 2.8–12.7) in group P and 8.0 months (95% CI, 4.7–15.6) in group PCT (p-0.41 for the comparison) (Figures 2A, 2B).

OS and TTD analysis in selected subgroups

We analyzed the treatment efficacy in several patient subgroups (Figures 3A-E, Supplementary Figures S1A-B). In the subgroup of 86 female patients, OS was significantly longer among those who received PCT (n = 22, mOS – not reached (NR), 95% CI, 11.4 months-NR) than among those who received P (n = 64, mOS-10.2 months, 95% CI, 6.8–17.2;

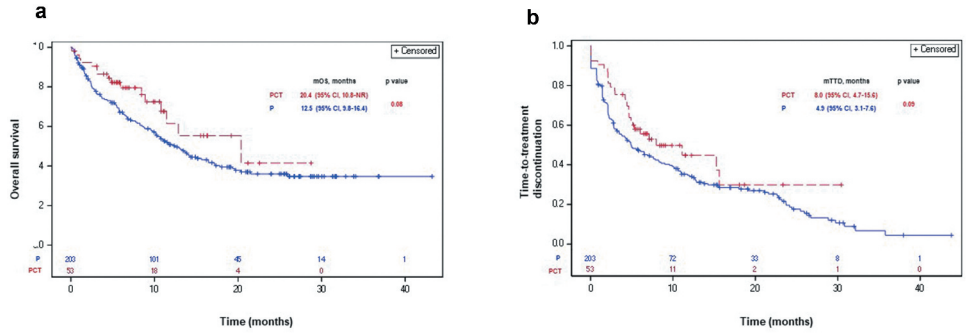

Figure 1. Overall survival (A) and time-to-treatment discontinuation (B) with 1st-line pembrolizumab or with 1st-line combination of pembrolizumab and platinum-based chemotherapy in patients with advanced non-small cell lung cancer with PD-L1 tumor proportion score ≥50% (n=256). *Abbreviations: mOS - median overall survival; mTTD - median time-to-treatment discontinuation; NR - not reached; P - pembrolizumab; PCT - combination of pembrolizumab with platinum-based chemotherapy*.

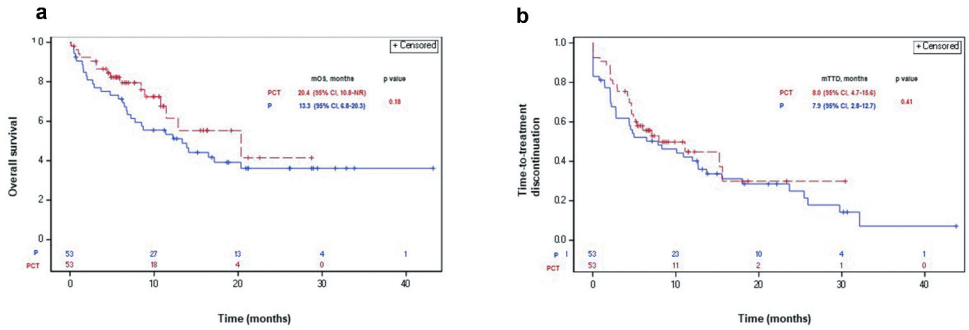

Figure 2. Overall survival (A) and time-to-treatment discontinuation (B) with 1st-line pembrolizumab or with 1st-line combination of pembrolizumab and platinum-based chemotherapy in patients with advanced non-small cell lung cancer with PD-L1 tumor proportion score ≥50% - matched for age, sex and ECOG PS (n=106). . *Abbreviations: mOS - median overall survival; mTTD - median time-to-treatment discontinuation; NR - not reached; P - pembrolizumab; PCT - combination of pembrolizumab with platinum-based chemotherapy*.

p-0.02), whereas in the subgroup of 170 male patients, OS was similar in those who received PCT (n = 31, mOS-12.9 months, 95% CI, 8.4-NR) and those who received P (n = 139, mOS-13.1 months, 95% CI, 10.1–19.3; *p* – 0.73) (Figures B1, B2). We next evaluated a potential impact of smoking on treatment effects. A non-significant trend for longer OS was seen in the PCT *vs* P group regardless of the smoking status. In the subgroup of 232 current/past smokers, mOS was 20.4 months in those who received PCT (n = 47, 95% CI, 10.8-NR) and 13.1 months in those who received P (n = 185, 95% CI, 10.1–-17.2; *p* – 0.17). Among the 21 never smokers, mOS was NR in those who received PCT (n = 5, 95% CI, 11.4 months-NR) and 9.5 months in those who received P (n = 16, 95% CI, 2.4–12.5; *p* – 0.16) (Figures C1, C2).

A similar non-significant trend for better OS in patients receiving PCT *vs* patients receiving P was seen in the rest of the examined subgroups. This included patients ≥65 years old (n = 150) and patients <65 years old (n = 106) (Figures A1, A2), patients with ECOG PS 0/1 (n = 182) and ECOG PS 2–4 (n = 71) (Figures D1, D2), tumors with PD-L1 90% >TPS≥50% (n = 92) and PD-L1 TPS ≥90% (n = 43) (Figures E1, E2), patients with liver metastases (n = 32), and without liver metastases (n = 224) (Figures S1A1, S1A2), and patients with brain metastases (n = 68), and patients without brain metastases (n = 187) (Figures S1B1, S1B2).

Univariate analysis of OS and TTD

In the univariate analysis, only ECOG PS ($p < .0001$) and age (*p*-0.0006) demonstrated a significant correlation with OS. The same factors: ECOG PS (*p*-0.0002) and age (*p*-0.009), as well as smoking history (*p*-0.003) were the only factors that significantly correlated with TTD. Type of 1st-line therapy (P *vs* PCT), sex, histological subtype, disease stage (IV *vs* III), tumor PD-L1 TPS (TPS ≥90% *vs* 90%>TPS≥50%), weight loss, and presence or absence of liver and brain metastases did not demonstrate a significant correlation with TTD or OS ($p > .1$) (Supplementary Table S2).

Safety

Significantly more patients experienced treatment-related adverse events with PCT as compared to P, including 49% and 31% of patients experiencing any grade adverse events (*p*-0.02), in groups PCT and P, respectively (Table 2). A numerical non-significant difference was also observed in

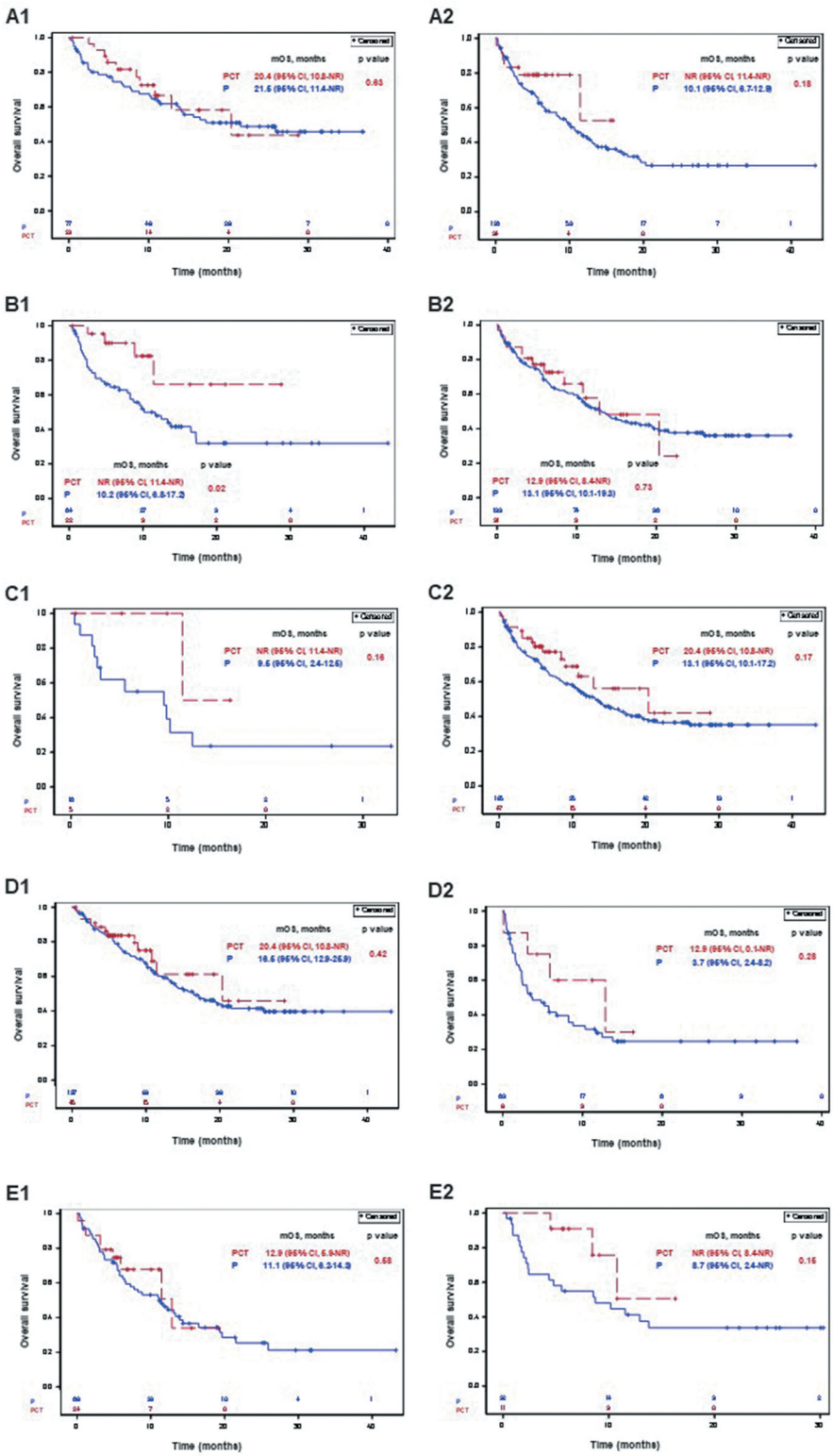

Figure 3. Overall survival analysis with 1st-line pembrolizumab or with 1st-line combination of pembrolizumab and platinum-based chemotherapy in selected subgroups of patients according to age (A1 - %< 65 years; A2 - ≥65 years), sex (B1 - females; B2 - males), smoking status (C1 - never smokers; C2 - past/current smokers), ECOG PS (D1 - ECOG PS 0-1; D2 - ECOG PS 2-4), and PD-L1 TPS (E1 - 90%>TPS≥50%; E2 - TPS ≥90%). *Abbreviations: ECOG PS - Eastern Cooperative Oncology Group performance status score; mOS - median overall survival; NR - not reached; P - pembrolizumab; PCT - combination of pembrolizumab with platinum-based chemotherapy; PD-L1 - programmed-death ligand 1; TPS - tumor proportion score.*

the rate of high-grade treatment-related adverse events (11% and 7% with PCT and P, respectively, p-0.26). Regarding specific adverse events, the incidence of neutropenia (<0.001) and oral mucositis (0.03) were significantly higher with PCT than with P. The rates of anemia, thrombocytopenia, fatigue, nausea, diarrhea, rash, creatinine elevation, AST/ALT elevation, and thromboembolic events were numerically higher with PCT as compared to P, although not in a statistically significant

Table 2. Treatment-related adverse events in patients with advanced non-small cell lung cancer and PD-L1 tumor proportion score ≥50% treated with 1st-line pembrolizumab (P) or with a combination of pembrolizumab and platinum-based chemotherapy (PCT) (statistically significant differences are underlined).

	Pts treated with P (n = 203)		Pts treated with PCT (n = 53)		
	Any Grade, n (%)	Grade ≥3, n (%)	Any Grade, n (%)	Grade ≥3, n (%)	p value (for any Grade)
Any AE	63 (31)	14 (7)	26 (49)	6 (11)	0.02
Neutropenia	0 (0)	0 (0)	8 (15)	2 (4)	≤0.001
Anemia	20 (10)	4 (2)	7 (13)	2 (4)	0.68
Thrombocytopenia	5 (2)	1 (0.5)	3 (6)	1 (2)	0.43
Fatigue	8 (4)	0 (0)	5 (9)	0 (0)	0.15
Mucositis oral	1 (0.5)	0 (0)	3 (6)	0 (0)	0.03
Nausea	3 (1)	1 (0.5)	1 (2)	0 (0)	0.76
Diarrhea	15 (7)	3 (1)	5 (9)	1 (2)	0.88
Rash	8 (4)	0 (0)	4 (7)	1 (2)	0.12
Endocrine irAE (thyroid, hypophysis)	3 (1)	0 (0)	0 (0)	0 (0)	1.00
Pneumonitis	5 (2)	0 (0)	0 (0)	0 (0)	0.59
ALT/AST elevation	11 (5)	2 (1)	6 (11)	0 (0)	0.13
Bilirubin elevation	4 (2)	0 (0)	0 (0)	0 (0)	0.58
Creatinine elevation	6 (3)	2 (1)	4 (7)	0 (0)	0.09
Arthritis	2 (1)	1 (0.5)	0 (0)	0 (0)	0.77
Myositis	1 (0.5)	1 (0.5)	0 (0)	0 (0)	1.00
Infusion related reaction	1 (0.5)	1 (0.5)	0 (0)	0 (0)	1.00
Flu like symptoms	3 (1)	0 (0)	0 (0)	0 (0)	1.00
Encephalitis	1 (0.5)	0 (0)	0 (0)	0 (0)	1.00
Vasculitis	0 (0)	0 (0)	1 (2)	0 (0)	0.21
Thromboembolic event	1 (0.5)	1 (0.5)	2 (4)	2 (4)	0.11

Abbreviations: AE – adverse events; ALT – alanine aminotransferase; AST – aspartate aminotransferase; irAE – immune-related adverse events; P – pembrolizumab; PCT – combination of pembrolizumab with platinum-based chemotherapy; PD-L1 – programmed-death ligand 1; pts – patients.

manner. The incidence of immune-related pneumonitis was 2% (grade 2) in group P and 0% in group PCT. The incidence of immune-related arthritis, myositis, encephalitis, vasculitis, and infusion-related reactions was low in both groups (Table 2).

Discussion

To the best of our knowledge, our study represents the first real-world-data based comparative analysis of pembrolizumab *vs* a combination of pembrolizumab with platinum-based chemotherapy in treatment-naïve *EGFR/ALK/ROS1*-wild-type PD-L1 TPS ≥50% aNSCLC patients. The importance of our study is further emphasized by the absence of randomized controlled clinical trials addressing the question.

We have observed no statistically significant difference in long-term outcomes (specifically, TTD and OS) between single-agent pembrolizumab and a combination of pembrolizumab and platinum-based chemotherapy. It should be noted that the combination of pembrolizumab and platinum-based chemotherapy demonstrated a statistically non-significant trend for better TTD and OS as compared to pembrolizumab alone. Importantly, a similar trend (in OS, not in TTD) have been observed in the propensity score matched groups, balanced for age, sex, and ECOG PS.

With regards to OS comparison, our observations are generally in line with the results obtained from the cross-trial comparisons of randomized clinical trials assessing each of the modalities and demonstrating similar survival rates for both pembrolizumab, atezolizumab, cemiplimab and the combinations of ICI with platinum-based chemotherapy in PD-L1 TPS ≥50% treatment-naïve aNSCLC.[2–12,14–16] These are further supported by different meta-analyses indirectly comparing the efficacy of pembrolizumab administered alone, or in combination with platinum-based chemotherapy, supporting the lack of OS advantage with the combined modality approach over pembrolizumab alone.[17–19] The trend for the numerically longer OS we observed with the combined therapy have several possible explanations. One of them is the fact that the large majority of patients that initiate single-agent ICI do not get an opportunity to benefit from chemotherapy in the subsequent treatment lines (specifically, in our analysis only 21% of patients progressing on pembrolizumab have received subsequent systemic treatments). Another possible explanation for the numerically shorter OS with pembrolizumab is the hyperprogression phenomenon during monotherapy with ICI. Indeed, the combined treatment is associated with higher ORR.[17,18]

While we have observed no statistically significant differences in TTD between the treatment groups, meta-analyses indicated a significantly longer PFS with the combined modality approach as opposed to pembrolizumab alone.[17–19] TTD by definition differs from PFS, as it includes treatment beyond progression, conceivably different between single-agent immunotherapy and combination treatment.

The combined treatment in our analysis was associated with higher rates of all-grades treatment-related adverse events, and specifically, neutropenia and mucositis.In terms of the toxicity profile comparison of the two strategies, our findings are not surprising, and resonate with the recently reported results of the CCTG BR.34 and CheckMate 227 trials. Both of these trials included acomparison of combined anti-PD-1/PD-L1+ anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) ICI therapy with the combination of these with platinum-based chemotherapy (for the CheckMate 227 trial– the combination of an anti-PD-1 agent with chemotherapy).[23,24] Ahigher rate of myelosuppression, anemia, fatigue, nausea and mucositis were seen with the chemotherapy-containing regimens. Importantly, in the CCTG BR.34 trial, the addition of platinum-based chemotherapy provided PFS advantage, however, was not associated with improvement in OS– which is in line with our observations and with the additional data discussed above.

We considered it potentially important to compare the efficacy of pembrolizumab and combination of pembrolizumab with platinum-based chemotherapy in selected patient subgroups. For instance, we hypothesized that the treatment effects might differ in patients with PD-L1 TPS ≥90% and 90% >TPS≥50%. Specifically, we expected to see no benefit from the addition of chemotherapy in patients with PD-L1 TPS ≥90%, while it was reasonable to suspect the existence of such a benefit in "less ICI beneficial" population of patients with 90%>TPS≥50%.[25] No such a correlation was observed. Additionally, no different impact of treatment choice (e.g.,

P or PCT) was demonstrated in subgroups selected by age, ECOG PS, presence of liver and brain metastases. These results, however, should be interpreted with caution since some of the subgroups (e.g., tumors with PD-L1 TPS ≥90%, patients with liver metastases) included less than twenty patients.

The only factor which seemed to interact with the treatment type was sex; in females, OS was significantly longer among those who received the combined therapy as compared to those who received pembrolizumab alone, whereas in males no differences were seen. Indeed, the sex-based heterogeneity in response to ICI was reported in several meta-analyses. For instance, Conforti et al. analyzed 20 trials evaluating ICI (mostly, administered as a single modality) in various malignancies, and discovered a smaller OS benefit with ICI in female patients (HR, 95% CI – 0.86, 0.79–0.93) in comparison with male patients (HR, 95% CI – 0.72, 0.65–0.79; *p*-0.0019).[26] A more complex picture with some inconsistent results were reported by Ye et al.[27] This meta-analysis, however, did not differentiate between the effects of ICI administered as a single modality and ICI administered in combination with chemotherapy. Zhou et al., analyzing additive effects of ICIs to the platinum-based chemotherapy in advanced NSCLC, reported on a larger OS benefit with the combinations in females (HR, 0.32) than in males (HR, 0.69, p for interaction < 0.001).[28] Conforti et al. performed another meta-analysis assessing the effects of sex on heterogeneity in response to ICI in advanced NSCLC, confirming that women derive larger benefit from the combination of ICI and platinum-based chemotherapy (HR, 95% CI – 0.44, 0.25–0.76 – for females *vs* HR, 95% CI – 0.76, 0.64–0.91 – for males; pooled HR, 95% CI – 1.70, 1.16–2.49). The opposite effect was observed with ICI alone compared to chemotherapy (HR, 95% CI – 0.97, 0.79–-1.19 – for females *vs* HR, 95% CI – 0.78, 0.60–1.00 – for males; pooled HR, 95% CI – 0.83, 0.65–1.06).[29] Additionally, a network meta-analysis of indirect comparisons of NSCLC trials performed by Dafni et al. indicated a larger PFS benefit with the combination of pembrolizumab and platinum-based chemotherapy *vs* nivolumab in females (p for interaction with sex – 0.0058).[19] The observed sex-related differences in the efficacy of the two ICI-based strategies might be related to different immune responses to stimuli in men and women. Such differences, among other factors might be attributable to X-chromosome-linked immune-related microRNAs, different estradiol and testosterone levels, or different microbiome profiles.[30]

Importantly, the sex-based OS heterogeneity observed in our analysis did not seem to be related to the smoking status. Again, never smokers were under-represented in our cohort, not allowing solid conclusions to be drawn regarding the comparative efficacy of pembrolizumab and the combined treatment in this important patient subset. Although tumors harboring *EGFR* sensitizing mutations and *ALK – and ROS1* – rearrangements were excluded from the analysis (in accordance with pembrolizumab labeling), comprehensive genomic profiling was only performed in limited number of cases. Therefore, the existence of an activating driver mutation in other genes as an underlying cause for the observed sex-related heterogeneity cannot be ruled out. TMB and microsatellite instability/mismatch repair deficiency have recently emerged as important predictive biomarkers of ICI efficacy.[13,22,31–33] Unfortunately, the lack of data with regards to TMB and microsatellite instability/mismatch repair deficiency for most patients in the selected cohort did not allow us to assess the correlation between these and the efficacy of the two ICI-based strategies.

The most important limitations of our study are its retrospective nature, relatively small sample size (especially in the cohort matched for baseline characteristics), and significantly shorter follow-up in the group receiving the combined treatment. The results of subgroups analyses, and specifically, the results obtained in females, representing 33% of patients in the original cohort, are only hypothesis-generating. An additional important limitation of our analysis is the inability to assess the efficacy of the two treatment regimens in accordance with the tumor burden. Such an assessment would require central radiological revision which, unfortunately could not be done. The inability to correlate the treatment efficacy with the TMB and microsatellite instability/mismatch repair deficiency status also represents an important limitation of the analysis. Our conclusions warrant confirmation in a large prospective randomized controlled trial; such a trial (INSIGNA trial – NCT03793179) is currently ongoing and is close to its recruitment goal.

Our analysis suggesting the lack of a significant OS advantage with the addition of platinum-based chemotherapy to ICI in treatment-naïve *EGFR/ALK/ROS1*-wild-type PD-L1 TPS ≥50% aNSCLC patients provides an additional justification for the use of ICI monotherapy in this patient subset. The non-significant trend for better outcomes with the combined treatment can only be regarded as hypothesis-generating. These observations need to be confirmed in a large prospective randomized trial addressing the comparative efficacy of the two treatment strategies in specific patient subgroups. Currently, the treatment decision in this patient subset should be individualized and should weigh the benefit of higher ORR of the combined treatment modality against the risk of chemotherapy-related adverse events, and should take into account patient sex, smoking status, disease tempo, and severity of the disease-related symptoms.

Disclosure of interests (all outside of the submitted work)

Elizabeth Dudnik reported personal fees for consulting or advisory services from MSD, BMS, Astra Zeneca, Roche, Boehringer Ingelheim, Pfizer, Novartis, Takeda. Mor Moskovitz reported personal fees for consulting or advisory services from Boehringer Ingelheim, Roche, Astra Zeneca, MSD, BMS, Pfizer, Novartis, Takeda. Damien Urban reported personal fees and non-financial support from BMS, personal fees from MSD, personal fees from Roche, personal fees and non-financial support from Astra Zeneca, personal fees and non-financial support from Takeda, personal fees from Boehringer Inglelheim. Mira Wollner reported personal fees for consulting or advisory services from Boehringer Ingelheim, Roche, Astra Zeneca, Pfizer, MSD, BMS, Takeda. Ofer Rotem reported personal fees from Boehringer Ingelheim, MSD, Astra Zeneca, Takeda. Alona Zer reported grants and personal fees from BMS, personal fees from Roche, MSD, Astra Zeneca. Sameh Daher reported personal fees from MSD, Roche, Astra

Zeneca, Boehringer Ingleheim. Jair Bar reported grants and personal fees from AstraZeneca, grants and personal fees from MSD, grants from OncoHost, grants from ImmuneAI, personal fees from Roche, Abbvie, BMS, Bayer, Boehringer Ingelheim, VBL, Novartis, Takeda.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Data accessibility

Data are not publicly available according to the Rabin Medical Center strict institutional policy with regards to public availability of unidentified patient data. However, that are minimally required to replicate the outcomes of the study will be made available upon reasonable request.

Ethical statement:

The study was conducted in accordance with the principles of good clinical practice, and institutional review board approval was obtained at each participating oncological center prior to study initiation. No patient identifying data was included in the central data collection. Ethical committee approval numbers at each of the 4 participating centers are as follows: RMC-0391-14, SMC-8990-11, SMC-3821-16, RMB-0220-16, HMO-0238-17.

Consent to participate

Since the study represents a retrospective analysis of data, and all the patient-related clinical information was fully anonymized during the data collection, a waiver from obtaining an informed consent was granted by the institutional review board in each participating center.

Consent for publication

The manuscript does not contain any individual person's data.

Authors' contributions

Elizabeth Dudnik, Mor Moskovitz, and Jair Bar have made substantial contribution to the conception and design of the work, acquisition and analysis of the data; all the listed authors contributed substantially to the interpretation of the data and manuscript drafting; all the listed authors revised the submitted manuscript and approved its final version before submission.

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